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[1]*Department of Physiological Science and* [2]*Brain Research Institute, University of California, Los Angeles 90095;* [3]*National Aeronautics and Space Administration Ames Research Center, Moffett Field, California 94035; and* [4]*National Aeronautics and Space Administration Johnson Space Center, Houston, Texas 77058*

McCall, G. E., C. Goulet, R. R. Roy, R. E. Grindeland, G. I. Boorman, A. J. Bigbee, J. A. Hodgson, M. C. Greenisen, and V. R. Edgerton. Spaceflight suppresses exercise-induced release of bioassayable growth hormone. *J. Appl. Physiol.* 87(3): 1207–1212, 1999.—We have reported that bed rest suppressed the release of bioassayable growth hormone (BGH) that normally occurs after an acute bout of unilateral plantar flexor exercise (G. E. McCall, C. Goulet, R. E. Grindeland, J. A. Hodgson, A. J. Bigbee, and V. R. Edgerton. *J. Appl. Physiol.* 83: 2086–2090, 1997). In the present study, the effects of spaceflight on the hormonal responses to this exercise protocol were examined. Four male astronauts on the National Aeronautics and Space Administration Shuttle Transport System (STS-78) mission completed the exercise protocol before, during, and after a 17-day spaceflight. The maximal voluntary contraction torque output at the onset of exercise was similar on all test days. Before spaceflight, plasma BGH increased 114–168% from pre- to postexercise. During spaceflight and after 2 days recovery at normal gravity (1 G), the BGH response to exercise was absent. After 4 days of recovery, this response was restored. Plasma concentrations of immunoassayable growth hormone were similar at all time points. The preexercise plasma immunoassayable insulin-like growth factor I (IGF-I) levels were elevated after 12 or 13 days of microgravity, and a ≈7% postexercise IGF-I increase was independent of this spaceflight effect. The suppression of the BGH response to exercise during spaceflight indicates that some minimum level of chronic neuromuscular activity and/or loading is necessary to maintain a normal exercise-induced BGH release. Moreover, these results suggest that there is a muscle afferent-pituitary axis that can modulate BGH release.

fatigue; human; maximum voluntary contraction; electromyography

EXERCISE STIMULATES the release of growth hormone (GH) in humans (25), whereas spaceflight has been reported to disrupt several aspects of pituitary GH function (10, 12, 13, 19). The responses of GH to exercise that have been reported seem to be complex, perhaps because there are a variety of circulating GH variants (2), most of which are measured by immunoassay (IGH), and others by bioassay (BGH) (6, 8, 15). Spaceflight or hindlimb suspension of rats decreased the secretion of BGH from pituitary cells in vivo and in vitro (10, 12). Also, plasma concentrations of BGH, but not IGH, increased after a brief series of unilateral isometric plantar flexor contractions in humans (15). This exercised-induced release of BGH was suppressed during bed rest, a ground-based model of human spaceflight, but returned within 2 or 3 days after restoration of ambulation. Thus BGH release seems to be stimulated by acute bouts of brief exercise, but this acute response is inhibited by chronic alterations in neuromuscular activation and/or loading such as occurs during bed rest. We also found that muscle afferent activity can modulate the release of BGH, but not IGH, from the pituitary in rats (8). Thus the suppression of exercise-induced BGH release during bed rest (15) may have been due to a functionally blunted muscle afferent-pituitary axis. Although there are a number of studies showing altered sensory thresholds or processing at normal gravity (1 G) after spaceflight (5), no evidence of afferent suppression of exercise-induced BGH release during or after spaceflight has been reported. Given that a weightless environment markedly alters proprioception and the patterns of neuromuscular activation associated with loading (5) and that bed rest suppresses the BGH response to exercise (15), we hypothesized that the exercise-induced BGH release in humans also would be disrupted during spaceflight.

To interpret the hormonal responses relative to the subject's ability to exert maximal efforts before, during, and after spaceflight, maximal and submaximal torque and the associated electromyographic (EMG) amplitudes of the soleus (Sol) and medial gastrocnemius (MG) muscles were recorded. Previous studies show that the "antigravity" postural muscles of the lower leg, i.e., the plantar flexors, are particularly affected by spaceflight (5). Atrophy of the plantar flexors would be expected to decrease maximal torque production, and, in conjunction with metabolic and contractile protein changes, also might alter muscle fatigability (4). Furthermore, there is evidence of some reorganization of the levels of activation of the Sol compared with the MG muscles during a specific motor task in rhesus monkeys during (18) and after spaceflight (11, 17, 18).

METHODS

Four male astronauts, 43.8 ± 3.8 yr of age, aboard the 17-day National Aeronautics and Space Administration Life and Microgravity Spacelab (LMS) Shuttle Transport System (STS-78) mission, performed a programmed series of unilateral isometric plantar flexor contractions (Fig. 1) at 30 and 12 days before launch (L−30 and −12), on *flight days 2* or *3* and

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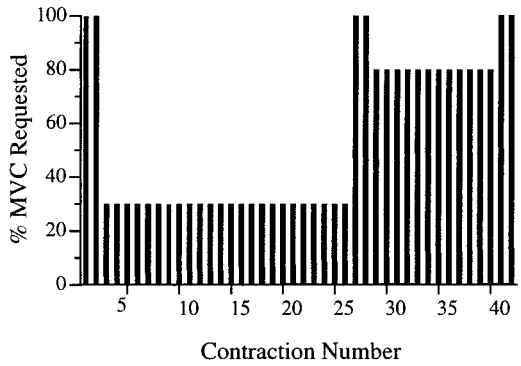

Fig. 1. Isometric plantar flexion exercise protocol. On each test day, maximal voluntary torque was obtained during a preceding reference test and used to establish torques for submaximal contractions performed during the exercise test. Each thin solid bar represents a contraction, with all contractions performed sequentially and at a 4:1-s work-to-rest ratio. Subjects received visual biofeedback from a computer monitor to produce requested submaximal torques.

13 or *14* (FD2 or 3 and FD13 or 14), and after 2, 4, 8, and 15 days of recovery (R+2, R+4, R+8, and R+15), respectively. Three identical torque-velocity dynamometers (Laboratory of the Swiss Federal Institute of Technology, Zurich, Switzerland) specifically designed for the shuttle's Spacelab were used for all testing. The right leg was used during all tests. The subjects laid supine with the joint angles of the tested leg fixed at 160° for the knee and 90° for the ankle. The foot, leg, and thigh were secured by a Velcro strapping system. A four-point shoulder-waist harness system was used to secure the upper body to a padded body plate. Figure 2 shows one of the crewmembers performing the exercise protocol inflight. Sol and MG EMG were recorded (sample rate: 1,000/s) by using disposable pregelled silver-silver chloride bipolar surface electrodes placed 2.5 cm apart (center to center) over the belly of the MG muscle, and in the midline below the junction of the two heads of the gastrocnemius for the Sol. To accurately reposition the electrodes between test days for each subject, electrode placement was standardized by creating an individualized pattern of electrode positioning in relation to anatomic landmarks and skin blemishes such as freckles. During flight, electrode positions determined before launch were marked daily with indelible ink. Before every testing session, EMG signals were verified by asking subjects to activate individual muscle groups to ensure proper signals as well as an absence of cross-talk between agonist and antagonist (tibialis anterior EMG also was recorded; data not shown) muscles. Torque and amplified EMG (gain: 1,000) signals were digitized and recorded directly onto a microcomputer hard drive. The maximal voluntary contraction (MVC) on a given test day was defined as the highest torque (Nm) of the two initial requested MVCs (Fig. 1). Similarly, the highest torque achieved for the two MVCs requested after each series of submaximal contractions was defined as the post-30% and -80% MVC, respectively. The maximum integrated burst of EMG corresponded to the interval during the 4-s contraction at which torque output was plateaued. EMG values for a given test day are expressed as a percentage of the EMG recorded during the highest initial MVC (mean rectified EMG of contraction/mean rectified EMG of initial MVC $\times$ 100).

Blood samples were collected by either an indwelling catheter or venipuncture before and immediately after completion of the exercise test. The method used for blood collection was a decision of the individual crew member and not the investigators. The majority of ground tests employed catheters, whereas venipunctures were primarily utilized during spaceflight as the crew encountered difficulties inserting and/or maintaining the catheters. The crew reported that most inflight samples were obtained within 2 min after completion of the test, but delays in obtaining a successful venipuncture resulted in one or two posttest samples being obtained 4–5 min after the test. All ground samples were collected between 1 and 2 min after completion of the test. Blood was collected into 6-ml lithium-heparin vacuum plasma-separation tubes (Terumo P204SPG, Somerset, NJ), centrifuged at 1,000 *g* for 20 min, and frozen (−20°C) until analysis. Because of scheduling constraints and/or conflicts with the many other experiments performed during the mission, control for dietary intake or the time of day the experiments were performed was not permitted for any test period. Details of the other experiments performed on the STS-78 mission can be found in National Aeronautics and Space Administration government publications (1, 3).

The GH bioassay of tibia epiphyseal cartilage growth in hypophysectomized rats was performed to measure BGH as previously described (9), with the following modifications because of the limited volumes of blood withdrawn (≤6.0 ml). To achieve the 6.0-ml of final volume required for the bioassay, 1.5–4.4 ml of plasma were diluted with 0.85% saline to a total volume of 7.0 ml. Injection of the plasma-saline solution proceeded over a 4-day period as previously described (9). The tibial-growth-promoting activity of the plasma, i.e., BGH, was expressed as the human equivalent (3 IU/mg) concentration (μg/l) of a standard purified bovine pituitary GH (1.5

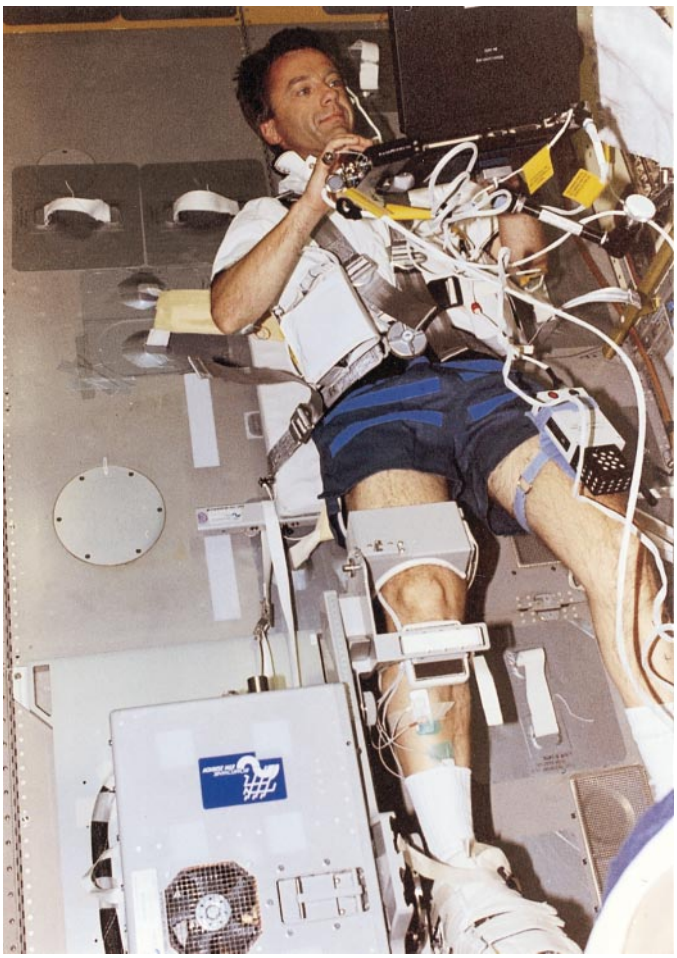

Fig. 2. Crew member aboard space shuttle is shown performing exercise protocol on Spacelab torque-velocity dynamometer.

IU/mg) after correction for the saline dilution. Saline-diluted samples were also assayed for IGH by using the procedure of Schalch and Reichlin (20) and subsequently corrected for saline dilution. Insulin-like growth factor I (IGF-I) concentration of undiluted plasma was measured after acid-ethanol extraction by using a commercial radioimmunoassay kit (Nichols Institute Diagnostics, San Juan Capistrano, CA). Differences within and between test days were compared by using a two-factor repeated-measures ANOVA. Multivariate ANOVA, which adjusts for the correlation because of repeated measurements in the same subjects, was not feasible because the number of repeated measures (3 MVCs for each of 6 test days = 18 MVCs; 2 blood samples for each of 8 test days = 16 blood samples) exceeded the total number of subjects ($n = 4$). Therefore, univariate analyses were performed by using the Greenhouse-Geisser procedure, which corrects for repeated measures by adjusting the *F*-value before the probability estimate. Test days with incomplete data sets were excluded from the statistical analyses (see RESULTS). Linear combination contrasts were used to compare between MVCs performed at the times indicated in Table 1. Pairwise contrasts were used to compare values within test days. Significant differences were established at $P < 0.05$.

RESULTS

Torque and EMG. During initial testing on FD2 or 3, the body plate was not adequately secured to the floor of the Spacelab, causing the plate to move backward when the subject exerted maximal efforts against the dynamometer. Because of this problem, the FD2 or 3 MVC data were considered invalid and excluded from the statistical analyses. This problem was remedied on subsequent test days by tethering the body plate and also having another crew member exert downward force on the body plate to prevent it from moving. On R+2 testing, the data file from one subject was corrupted, and no data were recoverable. Therefore, the R+2 results were not included in the statistical analyses.

Plantar flexor torque produced during the initial MVCs were similar before, during, and after spaceflight (Table 1). The MVCs performed after the series of 30% MVC contractions were similar to the initial MVC (92–104% of initial MVC). Repetitive submaximal contractions at 80% MVC decreased the torque of the post-80% MVCs (82–94% of initial MVC; $P < 0.05$) before, during, and after spaceflight. The Sol and MG EMG amplitudes and the EMG-to-torque ratios were similar between the initial MVCs and the post-30% and -80% MVCs. The Sol/MG EMG ratios also were similar during all MVCs (range: 0.97 ± 0.12 to 1.19 ± 0.48), as well as among the submaximal contractions performed at the beginning, middle, and end of the 30% MVC series (range: 0.71 ± 0.39 to 1.32 ± 0.46), and the beginning and end of the 80% MVC series (range: 0.91 ± 0.31 to 1.13 ± 0.41).

Hormonal responses. During the preflight experiments, the plasma concentrations of BGH were elevated after exercise (Fig. 3*A*). This exercise-induced release of BGH was absent during spaceflight and early recovery (R+2), whereas this response was restored by 4 days after return to 1 G. The preexercise BGH levels were similar among all test days. Plasma IGH concentrations were similar before and after exercise and were unaffected by spaceflight (Fig. 3*B*). Spaceflight differentially affected the IGH and BGH response to exercise (see Fig. 5).

There was a significant main effect for an increase in plasma immunoassayable IGF-I after exercise, and this response was independent of spaceflight (Fig. 4). Baseline preexercise plasma immunoassayable IGF-I levels

Table 1. *Plantar flexor torque and electromyographic activity of the soleus and medial gastrocnemius muscles during maximal voluntary contractions*

	L−30	L−12	FD13 or 14	R+4	R+8	R+15
MVC torque, Nm						
Initial MVC	165 ± 37	175 ± 24	187 ± 8	190 ± 19	185 ± 21	200 ± 12
Post-30% series	161 ± 32	182 ± 24	178 ± 3	180 ± 18	181 ± 20	195 ± 15
Post-80% series*	153 ± 31	157 ± 14	157 ± 9	155 ± 21	174 ± 19	176 ± 23
Sol EMG						
Post-30% series						
%Initial MVC	96 ± 19	102 ± 9	104 ± 25	81 ± 9	93 ± 18	88 ± 9
EMG-to-torque ratio	1.00 ± 0.23	0.98 ± 0.07	1.08 ± 0.23	0.85 ± 0.09	0.95 ± 0.19	0.91 ± 0.09
Post-80% series						
%Initial MVC	101 ± 28	100 ± 17	105 ± 23	85 ± 17	92 ± 15	93 ± 6
EMG-to-torque ratio	1.08 ± 0.21	1.10 ± 0.08	1.23 ± 0.18	1.05 ± 0.22	0.98 ± 0.12	1.06 ± 0.14
MG EMG						
Post-30% series						
%Initial MVC	103 ± 27	96 ± 17	92 ± 19	79 ± 12	96 ± 12	85 ± 3
EMG-to-torque ratio	1.06 ± 0.25	0.92 ± 0.15	0.97 ± 0.22	0.83 ± 0.11	0.99 ± 0.13	0.88 ± 0.04
Post-80% series						
%Initial MVC	99 ± 15	99 ± 19	109 ± 11	74 ± 14	87 ± 15	81 ± 16
EMG-to-torque ratio	1.08 ± 0.14	1.10 ± 0.23	1.31 ± 0.23	0.90 ± 0.09	0.93 ± 0.17	0.92 ± 0.15

Values are means ± SD; $n = 4$ subjects. L, launch; FD, flight day; R, recovery; MVC, maximal voluntary contraction; Sol, soleus; EMG, electromyographic activity; MG, medial gastrocnemius; post-30% and -80% series, after submaximal series of contractions. EMG values are expressed as defined in METHODS. Before calculation of the EMG-to-torque ratio, the torque was expressed as a percentage of the torque recorded during the highest of the two initial MVCs (Fig. 2). FD2 or 3 and R+2 data are excluded from these analyses as explained in RESULTS. *Significant main effect among MVCs (ANOVA, $P < 0.05$), with the post-80% series significantly decreased as compared with the initial MVC or the post-30% series (linear combination contrasts, $P < 0.01$).

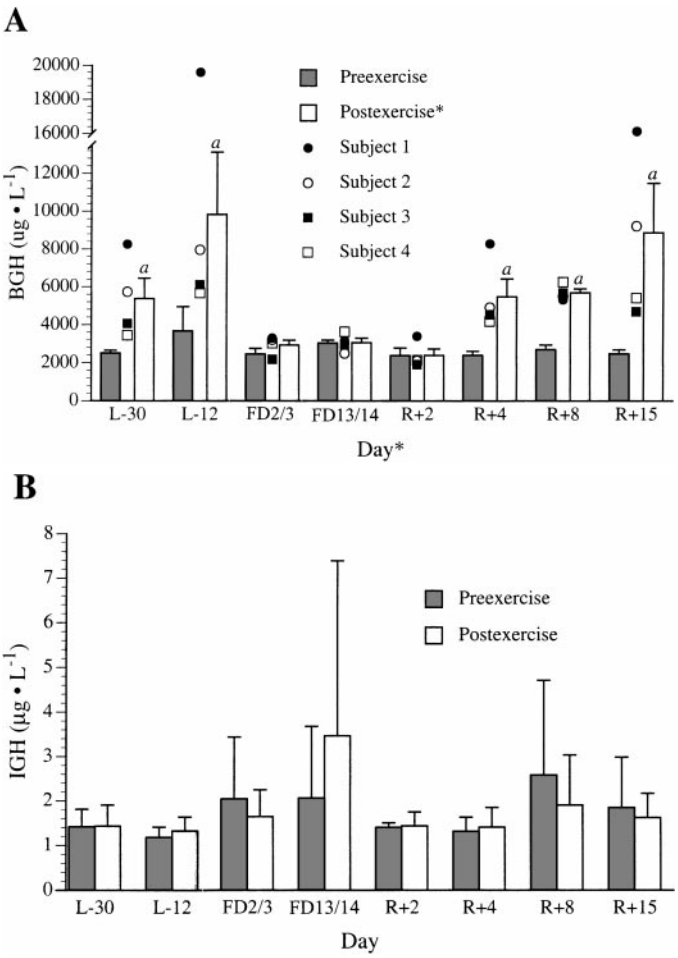

Fig. 3. Bioassayable (BGH; *A*) and immunoassayable (IGH; *B*) growth hormone plasma concentrations before (preexercise) and after (postexercise) the exercise test. Values are means ± SD. For BGH, postexercise data for each subject are depicted by symbols. Preflight test days occurred 30 (L−30) and 12 (L−12) days before launch (L). During flight, testing occurred on either *flight day 2* or *3* (FD2 or 3) and was repeated on either *flight day 13* or *14* (FD13 or 14). Postflight test days occurred 2 (R+2), 4 (R+4), 8 (R+8), and 15 (R+15) days during recovery (R) at 1 G. *Significant main and interaction effects (ANOVA; $P < 0.05$). [a]Significant difference between pre- and postexercise on a given day (pairwise contrast; $P < 0.05$). There were no significant effects for IGH.

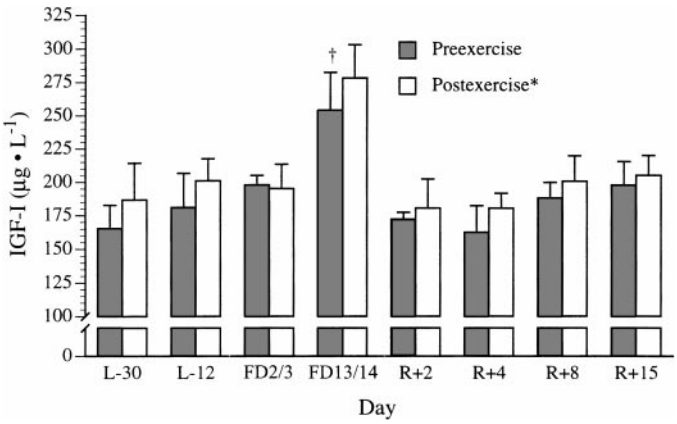

Fig. 4. Immunoassayable IGF-I plasma concentrations preexercise and postexercise. Values are means ± SD. Test days are the same as in Fig. 3. *Significant main effect from pre- to postexercise (ANOVA; $P < 0.05$). †Significantly different from all other preexercise values (pairwise contrasts; $P < 0.05$).

were higher after 13 or 14 days exposure to microgravity compared with all other test days.

DISCUSSION

Although a wide range of hormone measurements have been made from blood (23) or urine (22) samples obtained from crew members before, during, or after a spaceflight mission, there have been no investigations of the endocrine response to a well-defined exercise perturbation imposed before, during, and after spaceflight. By studying the hormonal responses to the same exercise protocol, we can begin to understand whether the regulatory mechanisms associated with an altered hormone concentration during spaceflight are activity and/or load dependent. We examined the effects of microgravity on the hormonal responses, specifically the GH/IGF-I axis, to resistance exercise. Although the maximum motor output (MVCs) of the plantar flexors was unaffected by 17 days of spaceflight, there was an absence of an exercise-induced plasma BGH response during spaceflight (Figs. 3*A* and 5). This effect was similar to that observed in a 17-day bed rest study (15). Similarly, the lack of an effect of either brief exercise or spaceflight on IGH levels (Figs. 3*B* and 5) was comparable to the bed rest results (15). These results indicate that circulating BGH and IGH have different response thresholds to exercise. The rapid exercise-induced BGH elevation may reflect a muscle afferent-pituitary axis that can regulate BGH release in rats (8). This axis presumably involves a presently uncharacterized muscle afferent pathway to the hypothalamic-pituitary areas that can modulate BGH release. In contrast, IGH responses are associated with exercise of greater duration and/or intensity than used in the present study and can be regulated by circulating adrenergic, cholinergic, and possibly metabolic and opioid factors (for review, see Ref. 7).

On FD2 or 3, the astronauts encountered problems securing the body plate to the Spacelab, thereby render-

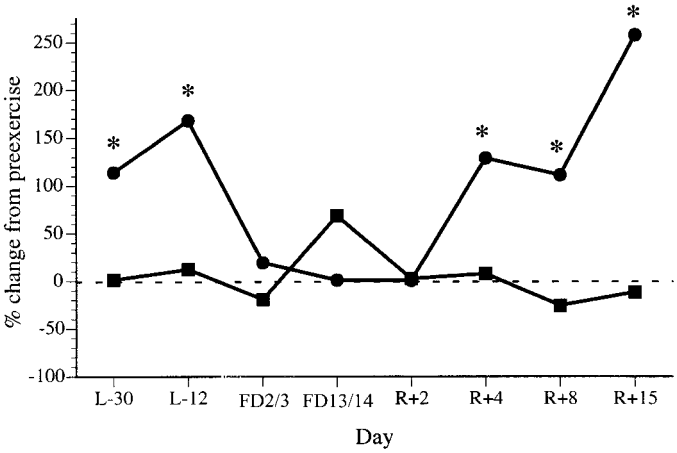

Fig. 5. Summary of magnitudes of IGH (■) and BGH (●) exercise-induced changes before, during, and after spaceflight. *Significant changes from pre- to postexercise ($P < 0.05$).

ing the MVC torque data for that test period invalid. It could be argued that the absence of a BGH response during the FD2 or 3 tests may have been due to the reduced MVC torque output, i.e., reduced exercise intensity. Although we cannot unequivocally rule out this possibility, this seems unlikely for the following reasons. Because the subjects were performing maximal voluntary efforts, it would appear that both efferent and afferent activation levels were maximal and that the problem was merely in the recording of the torque output. Second, a BGH response is elicited in a 1-G environment during brief protocols of submaximal isometric plantar flexion at 30 or 80% MVC lasting 5 or 1 min, respectively (15). Therefore, the exercise protocol in the present study (Fig. 1), even if it was performed at a reduced intensity during FD2 or 3 testing, should have been sufficient to elicit a BGH response at 1 G.

The depressed BGH exercise response during early recovery (R+2) from spaceflight (Figs. 3*A* and 5) was not observed at a comparable time point in the bed-rest study (15). If neuromuscular function was decreased during early recovery from spaceflight, but not bed rest (15), this could explain the disparity between these studies. Although the loss of MVC and EMG data from one of the subjects on R+2 precluded this time point from the statistical analyses in the present study, there were no indications of decreased neuromuscular function, e.g., decreased MVC and/or altered EMG activity, in the remaining three subjects. Thus the absence of BGH release during early recovery from spaceflight was not due to a decreased neuromuscular function. Alternatively, the disparity between these studies might be explained by differences in the experimental paradigms. Because a muscle afferent-pituitary axis has been hypothesized as one regulatory pathway for BGH release in both humans (15) and rats (8), this differential response might be indicative of a greater qualitative and/or quantitative disruption of proprioceptive input by microgravity compared with bed rest. Consistent with this suggestion are reports indicating that basal somatotroph BGH synthesis and/or secretion in rats is reduced after spaceflight (10, 12) as well as hypothalamic GH-releasing hormone (GHRH) expression and synthesis (19). Moreover, when rat pituitary cell cultures were flown in space, GHRH-stimulated BGH release was reduced after return to 1 G (13), indicating that microgravity also impairs somatotroph cell functioning independently of the proposed afferent pathway(s). Similar afferent-independent alterations in cellular BGH regulation, if they occur in humans exposed to microgravity, also could have contributed to the absence of an exercise-induced BGH response during spaceflight and early recovery at 1 G.

Although the ANOVA showed a significant main effect for the small increase in immunoassayable IGF-I pre- to postexercise, the absence of a main effect for flight day or of an interaction effect indicated that this response was not a function of spaceflight. Thus the lack of a BGH-exercise response during spaceflight and early recovery as measured by the tibial assay could not be attributable to differential immunoassayable IGF-I responses. The increased baseline circulating immunoassayable IGF-I levels after 13- or 14-day exposure to microgravity have not been reported previously. An increase in circulating immunoassayable IGF-I typically reflects a GH-mediated increase in hepatic IGF-I production, resulting from a sustained elevation of circulating GH. However, the consensus from the limited prior data is that circulating GH and IGF-I are not elevated by spaceflight in humans (23). Additionally, Stein et al. (22) recently reported that urinary immunoassayable IGF-I and IGH excretion were unchanged by spaceflight. Thus the reason(s) for the immunoassayable IGF-I elevation during spaceflight in the present study is not evident because microgravity had no effect on baseline IGH or BGH concentrations and also eliminated the BGH exercise response.

The exercise protocol induced a similar degree of modest fatigue on all test days, as evidenced by the significant reduction in maximal torque output for the post-80% MVCs. The EMG amplitudes of the Sol and MG muscles were similar during all MVCs, indicating comparable neural activation during maximal efforts before, during, and after spaceflight. Despite the maintenance of EMG amplitudes and decreased torque during MVCs performed after repetitive submaximal contractions, the EMG-to-torque ratios of the Sol and MG were similar during all MVCs. The Sol-to-MG EMG ratios were also similar during submaximal or maximal contractions at all time points. Therefore, alterations in the relative contribution of the Sol and MG observed in rhesus monkeys performing nonmaximal motor activities during (18) and after spaceflight (11, 17, 18) were not observed during submaximal or maximal plantar flexion in humans during or after spaceflight.

The clear depression of the exercise-induced BGH response to brief unilateral plantar flexion during spaceflight is intriguing given the maintenance of torque potential of this same muscle group. The absence of a spaceflight effect on neuromuscular function in the present study could reflect a countermeasure effect from the cumulative volume or patterns of plantar flexor muscle contractions performed during the numerous flight investigations. Indeed, preliminary data from a recent 17-day unilateral limb-suspension study in humans employing a regimen of exercises simulating all of the physiological testing performed during the LMS STS-78 mission reported that this level of activity was an effective countermeasure for the maintenance of neuromuscular function (21). Preliminary reports from a 17-day bed-rest study that employed exercise protocols comparable to those in the present study also indicated that no loss of maximal plantar flexor isometric torque occurred during or after bed rest (24). Thus exercise-induced BGH release, but not torque output, was impaired during both spaceflight and bed rest studies of comparable duration and activity levels. The reason(s) for the difference in the effectiveness of the exercise countermeasure on the efferent (EMG activity and torque output) and presumed afferent (BGH regulation) functions remains to

be elucidated, but intuitively it appears that these functions do not show the same mechanisms of control.

In conclusion, the depression of an exercise-induced BGH release during spaceflight in the present study combined with similar findings in a prior bed rest study (15) indicate that reductions in the chronic levels of neuromuscular activation and/or loading severely blunt the exercise-induced release of BGH even when maximal voluntary force output is maintained. The pathways via which brief exercise of one muscle group induces a release of BGH, and the identification and characteristics of the BGH molecule(s), remain to be determined. Moreover, the physiological effects that this change in BGH normally has beyond, perhaps, modulating bone growth are unknown. The significance of these results is the suggestion that proprioceptive neural input from the lower limbs to the hypothalamus and/or pituitary can be completely suppressed by chronic unloading. A persistence of this endocrine effect during long-term space missions could alter a variety of homeostatic mechanisms for the neuromusculoskeletal systems.

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REFERENCES

1. **Arnaud, S. B., K. Walker, and A. Hargens.** *Life and Microgravity Sciences Spacelab Mission: Human Research Pilot Study Six Month Report*, edited by S. B. Arnaud, K. Walker, and A. Hargens. Moffett Field, CA: NASA Ames Research Center, 1996. (NASA TM-110395)
2. **Baumann, G.** Growth hormone heterogeneity: genes, isohormones, variants, and binding proteins. *Endocr. Rev*. 12: 424–449, 1991.
3. **Downey, J. P.** *Life and Microgravity Spacelab (LMS) Final Report. Life and Microgravity Spacelab*, edited by J. P. Downey. Montreal, PQ, Canada: NASA/CP-1998–206960, 1998, p. iii-619.
4. **Edgerton, V. R., and R. R. Roy.** Neuromuscular adaptation to actual and simulated weightlessness. In: *Advances in Space Biology and Medicine*, edited by S. L. Bonting. Greenwich, CT: JAI, 1994, p. 33–67.
5. **Edgerton, V. R., and R. R. Roy.** Neuromuscular adaptations to actual and simulated spaceflight. In: *Handbook of Physiology. Environmental Physiology*. Bethesda, MD: Am. Physiol Soc., 1996, sect. 4, vol. I, chapt. 32, p. 721–764.
6. **Ellis, S., M. A. Vodian, and R. E. Grindeland.** Studies on the bioassayable growth hormone-like activity of plasma. *Recent Prog. Horm. Res*. 34: 213–238, 1978.
7. **Giustina, A., and J. D. Veldhuis.** Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. *Endocr. Rev*. 19: 717–797, 1998.
8. **Gosselink, K. L., R. E. Grindeland, R. R. Roy, H. Zhong, A. J. Bigbee, E. J. Grossman, and V. R. Edgerton.** Skeletal muscle afferent regulation of bioassayable growth hormone in the rat pituitary. *J. Appl. Physiol*. 84: 1425–1430, 1998.
9. **Greenspan, F. S., C. H. Li, M. E. Simpson, and H. M. Evans.** Bioasay of hypophyseal growth hormone: the tibial test. *Endocrinology* 45: 455–463, 1949.
10. **Grindeland, R., W. C. Hymer, M. Farrington, T. Fast, C. Hayes, K. Motter, L. Patil, and M. Vasques.** Changes in pituitary growth hormone cells prepared from rats flown on Spacelab 3. *Am. J. Physiol*. 252 (*Regulatory Integrative Comp. Physiol*. 21): R209–R215, 1987.
11. **Hodgson, J. A., S. C. Bodine-Fowler, R. R. Roy, R. D. de Leon, C. P. de Guzman, I. Koslovskaya, M. Sirota, and V. R. Edgerton.** Changes in recruitment of rhesus soleus and gastrocnemius muscles following a 14 day spaceflight. *Physiologist* 34, *Suppl*.: S102–S103, 1991.
12. **Hymer, W. C., R. Grindeland, I. Krasnov, I. Victorov, K. Motter, P. Mukherjee, K. Shellenberger, and M. Vasques.** Effects of spaceflight on rat pituitary cell function. *J. Appl. Physiol*. 73, *Suppl*.: 151S–157S, 1992.
13. **Hymer, W. C., R. E. Grindeland, T. Salada, P. Nye, E. J. Grossman, and P. K. Lane.** Experimental modification of rat pituitary growth hormone cell function during and after spaceflight. *J. Appl. Physiol*. 80: 955–970, 1996.
14. **McCall, G. E., C. Goulet, G. I. Boorman, J. A. Hodgson, R. R. Roy, and V. R. Edgerton.** Maintenance of plantarflexor muscle function in humans during a 17-day spaceflight (Abstract). *Med. Sci. Sports Exerc*. 29: S28, 1997.
15. **McCall, G. E., C. Goulet, R. E. Grindeland, J. A. Hodgson, A. J. Bigbee, and V. R. Edgerton.** Bed rest suppresses bioassayable growth hormone release in response to muscle activity. *J. Appl. Physiol*. 83: 2086–2090, 1997.
16. **McCall, G. E., C. Goulet, J. A. Hodgson, R. E. Grindeland, A. J. Bigbee, and V. R. Edgerton.** Spaceflight prevents release of bioassayable growth hormone in response to muscle activity (Abstract). *Neuroscience* 23: 1252, 1997.
17. **Recktenwald, M. R., J. A. Hodgson, R. R. Roy, S. Riazanski, G. E. McCall, I. Kozlovskaya, D. A. Washburn, J. W. Fanton, and V. R. Edgerton.** Effects of spaceflight on Rhesus quadrupedal locomotion after return to 1G. *J. Neurophysiol*. 81: 2451–2463, 1999.
18. **Roy, R. R., J. A. Hodgson, J. Aragon, M. K. Day, I. B. Koslovskaya, and V. R. Edgerton.** Recruitment of the Rhesus soleus and medial gastrocnemius before, during and after spaceflight. *J. Grav. Physiol*. 3: 11–16, 1996.
19. **Sawchenko, P. E., C. Arias, I. Krasnov, R. E. Grindeland, and W. Vale.** Effects of spaceflight on hypothalamic peptide systems controlling pituitary growth hormone dynamics. *J. Appl. Physiol*. 73, *Suppl*.: 158S–165S, 1992.
20. **Schalch, D. S., and S. Reichlin.** Plasma growth hormone concentration in the rat determined by radioimmunoassay: influence of sex, pregnancy, lactation, anesthesia, hypophysectomy and extrasellar pituitary transplants. *Endocrinology* 79: 275–280, 1966.
21. **Sheffield-Moore, M., K. R. Short, S. W. Trappe, K. E. Schulze, and D. L. Costill.** Resistance and aerobic exercise maintains skeletal muscle function and size in humans during simulated weightlessness (Abstract). *Med. Sci. Sports Exerc*. 30: S267, 1998.
22. **Stein, T. P., M. D. Schluter, and L. L. Moldwater.** Endocrine relationships during human spaceflight. *Am. J. Physiol*. 276 (*Endocrinol. Metab*. 39): E155–E162, 1999.
23. **Tipton, C. M., J. E. Greenleaf, and C. G. Jackson.** Neuroendocrine and immune system responses with spaceflights. *Med. Sci. Sports Exerc*. 28: 988–998, 1996.
24. **Trappe, S. W., T. A. Trappe, D. L. Costill, and R. H. Fitts.** Human calf muscle function in response to 17 days of bedrest (Abstract). Med. *Sci. Sports Exerc*. 28: S146, 1996.
25. **Vanhelder, W. P., R. C. Goode, and M. W. Radomski.** Effect of anaerobic and aerobic exercise of equal duration and work expenditure on plasma growth hormone levels. *Eur. J. Appl. Physiol*. 52: 255–257, 1984.